options as I saw them, taking into account the UK situation, the U.S., and the various approaches that we could use. It's a fairly long list because there were several options I was considering.

The first of these, we knew that the organism had restricted growth when it was stored in the refrigerator, cold, so one possibility was to get the show back on the road, having come to a screeching halt. Why don't we launch the product with a four-degree restriction? It would overcome the product with the microbial contamination proliferation. The disadvantage is that, going back to the patient that has to use the product, the patient would have to store it in the refrigerator, less than ideal. Also, it may have given ranitidine an undeserved reputation for instability. The four-degree storage wouldn't have been due to ranitidine, it would be because of the bug problem. Four-degree storage was possible but not favored.

The next option on my list here is with ethanol, ether alcohol. We had at that time done testing to show that the inclusion of alcohol killed the microorganism. But the next stage was to check whether it was medically acceptable. If we have a patient with an ulcer, it's not the best thing to do to add alcohol to the medicine for treating the ulcer. We know that alcohol can irritate ulcers. So that needed to be checked out.

Also the stability, if we add another ingredient stability could be compromised, not just the ranitidine, but any other aspect of the formulation.

Then we also had to check not just using ethanol but we had a number of different attempts at preserving the syrup. We had the first attempt with three parabens and we had the, later we had the later formulation where one of the preservatives was removed. We had to decide if we go with alcohol, do we go to the original formulation or do we go to the second? That was another consideration.

And then, always aware of the fact this project had come to a screeching halt, wanting to get the show back on the road quickly, I had to move fast. So looking at timetables here, if ethanol is okay, we would set up some stability batches in mid-September, analyze after three months storage, report the results, take it to our international standards committee. This is a committee that oversees every new formulation standards that we do for the company to make sure the standards are suitable for the use throughout the Glaxo Wellcome Group, and those standards are commonly in excess of national standards.

Then that covers the UK perspective.

From the U.S., we had two choices. One was similar to the UK, we could put the NDA in with the four-degree restriction, store in the refrigerator with the same

advantages and disadvantages I outlined before, and the other option was to advise our colleagues in the States that we could go for what is known as a creamer pack. A creamer pack, I don't know if you're familiar with a creamer pack commonly used to store milk, where you pour, tear the top off and tip it into the coffee, individual packs. I don't know what you call them in the States; we call them creamer packs in the UK. That package would be what's known as a unit dose pack. The top is tall and there's one dose in there, whereas the bottle is a multidose pack and during the use of that is the opportunity to remove syrup and get contamination.

If we had a creamer pack, the manufacturer could be controlled within the factory and the pack would be used once only, so there isn't the problem of the in-use contamination; take off the top, use the product and discard. So that was an option. However, the marketing requirements for the States were for a multiple-dose product, so we needed to get back to produce a formulation suitable for a bottle for multiple use.

The other consideration and option I was looking at, apart from ethanol, there are a range of other antimicrobial preservatives that I considered, bearing in mind that ethanol may have given problems stability-wise, there may have been medical objections to it, so I wanted another few shots in the locker as backups. Listed on this

page are some of the things that I was thinking of. These are handwritten notes from my own files. One is written, as chlorhexidine, C-H-L-O-R-H-E-X-I-D-I-N-E. I have two question marks against that. I, I indicated that wasn't my suggestion, somebody else said why don't you choose this. My instinctive reaction to that is, I have written here, try to kill it, done, IC toxicity. That's an example of where a possible preservative had been suggested but because it's toxic when taken by mouth it could be immediately thrown out.

At this stage I cast a very broad net, very broad net, and acted quickly to work medically to work through the possible preservatives. Some were thrown out very quickly. There is an example there. Another one is phenoxyethanol that is listed here.

THE COURT: Spell that.

A P-H-E-N-O-X-Y-E-T-H-A-N-O-L. In the, in reading the literature we discovered this one is specifically designed to kill *Pseudomonas cepacia*, which was obviously very attractive to us. It could be a winner. The question mark here on this one, it had an unknown action at the pH of 7. We didn't know how it would behave at that pH. That's a common factor in any antimicrobial preservative, the efficacy depends on the pH. Some are better at low pH, some are better at high. That really is an underlying thing for this case. The pH runs about 7 for ranitidine stability is one of the worst pHs

to get a preservative to work. It's a fairly restricted range, which is why we have a history of the problems.

So with phenoxyethanol we actually tried it and it did kill the bugs. Then a consideration there was what did it taste like? Always in this operation we're going through was what was the background, has it been used before, does it kill bugs; then we get to secondary considerations, what does it taste like. That comes back to the patient. The most important person in all of this is the patient. It's no use having a wonderfully stable product, the bugs are dead, but the patient doesn't like the taste.

So phenoxyethanol did kill the bugs. We kept it in reserve because we then found that ethanol did the job and probably phenoxyethanol could be used even today. We have found no reason for not using it.

Some preservatives I looked at, one there, it's benzalkonium chloride, B-E-N-Z-A-L-K-O-N-I-U-M, chloride, this is an example of where I was using imagination. There is no precedent for using this product by mouth, but I have worked on other products where this ingredient was used as a preservative for a product to go into the eye or into the nose, and the product delivered to the eye or the nose, some of it goes down the back of the throat into the digestive system, so there was a tenuous precedent for using benzalkonium chloride. My thought is what does it taste

like, has anybody tasted benzalkonium chloride? Does it kill the microorganism? We would need extra analytical methods for this ingredient. Would it cause, I have written here stringiness. This is another factor, another phenomenon that can occur in this type of product. The product is thickened with a cellose and the cellose with certain ingredients can decide to throw out a solution to form bits of string and gel, very inelegant.

A final consideration of benzalkonium chloride is what is the toxicology? How acceptable is it to take this material by mouth?

THE COURT: Doctor, what did you mean by extra analytical study?

THE WITNESS: In common with any ingredient we add, it will have to be analyzed as part of the specification of that product, as part of control. Because having introduced an ingredient to kill microorganisms, we needed to know at the time of manufacture is there enough in there, is there the right amount in there and also during storage is there still a sufficient level to maintain the quality of the product.

THE COURT: That would have been true about any --

THE WITNESS: It would have been true of any of them, right. We did try benzalkonium chloride and immediately got a crystalline precipitate. This is part of

science, it's part of discovery. We rationalized it afterwards. What happened is the benzalkonium chloride had complexed with the saccharin sodium, which is the sweetening agent. That is a nice example of what I mentioned yesterday where we have eleven ingredients and add a twelfth to this cocktail and anything could happen. It did in this case. If we have an incompatibility between two ingredients, we would discount the one that was being suggested as a new introduction.

So the one other is listed here, phenol. Keeping a very broad perspective on this, we knew that phenol was used in the injection, the Zantac injection. That means it's compatible with ranitidine. Two questions: Does it kill the bug and can we take it by mouth? Plus some of the other questions I mentioned before, what did it taste like? And we did an experiment, I believe it was about point 1 percent, with phenol. I believe it did kill the bugs but there was an antiseptic taste of phenol showing through the Zantac Syrup. In that example the question I posed was how low can we take phenol and still kill the bugs, plus is phenol acceptable when given by mouth? There is no precedent for it. We took that no further because by that time we had solved the issue with ethanol.

We had something like ten different options bubbling away and ethanol won the race and that describes how